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Original Contribution

Risk of Malaria Reemergence in Southern France: Testing Scenarios with a Multiagent Simulation Model

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Abstract: The Camargue, a region in southern France, is considered a potential site for malaria reemergence. All the suitable factors of the disease transmission system are present—competent mosquito vectors, habitats for their breeding, and susceptible people—except for the parasite. The objective of this study was to test potential drivers of malaria reemergence in this system after possible changes in biological attributes of vectors, agricultural practices, land use, tourism activities, and climate. Scenarios of plausible futures were formulated and then simulated using a spatially explicit and dynamic multiagent simulation: the MALCAM model. Scenarios were developed by varying the value of model inputs. Model outputs were compared based on the contact rate between people and potential malaria vectors, and the number of new infections in case of reintroduction of the parasite in the region. Model simulations showed that the risk of malaria reemergence is low in the Camargue. If the disease would reemerge, it would be the result of a combination of unfavorable conditions: introduction of a large population of infectious people or mosquitoes, combined with high levels of people–vector contacts resulting from significant changes in land use, tourism activities, agricultural policies, biological evolution of mosquitoes, and climate changes. The representation in the MALCAM model of interactions and feedbacks between different agents, and between agents and their environment, led in some cases to counterintuitive results. Results from scenario analyses can help local public health authorities in policy formulation.

Keywords: malaria, scenario, Camargue, multiagent simulation, disease emergence, land use

INTRODUCTION

The southern region of France, the Camargue, is considered as a potential site for malaria reemergence. It is currently malaria-free but large populations of competent malaria vectors, mosquitoes of the genus *Anopheles* (Diptera: Culicidae), are found in the region (Rodhain and Charmot, 1982; Alten et al., 2007; Ponçon et al., 2007a). Even if the risk of reemergence is low (Ponçon et al., 2007a), two cases of autochthonous transmission were suspected in southern France in 2006 (Doudier et al., 2007). Various factors could influence this reemergence, including climate and land-use changes.

Evaluating the risk of potential emergence or reemergence of vector-borne diseases requires imagining what could happen in the future. How could the environment

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change in the coming decades? What will be the impact of these changes on the risk of disease transmission? Scenario analysis was developed widely in business and environmental sciences to learn about the future. Scenarios are qualitative or quantitative "descriptions of possible futures" (van Notten et al., 2003). They are "neither predictions, nor forecasts, but an alternative image of how the future might unfold" (Nakicenovic et al., 2000). Van Notten et al. (2003) proposed an updated scenario typology. The most commonly used scenarios are the emissions scenarios (SRES) of the Intergovernmental Panel on Climate Change (IPCC) (Nakicenovic et al., 2000), and the recent Millennium Ecosystem Assessment Scenarios (Carpenter et al., 2005). The future of vector-borne diseases has already been analyzed, based on scenarios mostly related to climate change (e.g., for malaria: Martens et al., 1999; Rogers and Randolph, 2000; Thomas et al., 2004; van Lieshout et al., 2004; Schröder and Schmidt, 2008; and for tick-borne diseases: Ogden et al., 2006, 2008).

The objective of this study was to explore the potential role of biological processes, the geographical setting (i.e., impact of land-use changes), and the social context (i.e., changes in tourist activities) in the risk of malaria reemergence in the Camargue. To test the role of these potential drivers, scenarios of plausible futures were formulated. We explored the evolution of the risk of malaria reemergence under various conditions. We also identified a set of minimum conditions required for a reemergence of malaria in the Camargue. The risk of malaria reemergence was mainly based on the contact rate between people and potential malaria vectors, or the human biting rate (Linard et al., 2008). We also tested scenarios on the reintroduction of the parasite in the region. The goal was not to predict the future, but to understand how the system would respond under different plausible scenarios of future changes.

Background

Study Zone

The Camargue is a wetland area located in the Rhone delta, in southern France. This area is covered by pools and marshes, and the omnipresence of water plays a crucial role in the regional development. The climate of the region is Mediterranean, with warm and dry summers and mild and wet winters. Our study zone, called "Carbonnière," is located on the outside edge of the national park of the Camargue, in the region called "Camargue gardoise." The zone is approximately 25 km^2 and includes the typical biotopes of the Camargue, principally different kinds of marshes and rice fields.

Entomological studies were performed in the study zone and highlighted the presence of one potential malaria vector: *Anopheles hyrcanus* (Ponçon et al., 2007a). The main breeding sites for this species are rice fields (Tran et al., 2008). Social surveys performed in the study zone identified five main activities: residence, cultivation (principally rice cultivation), cattle raising, hunting, and tourism (Langewiesche, 2005). Each activity is associated with a land use. Rapid land-use changes were observed in the Camargue during the past decades and are expected to continue in the future (Dervieux, 2005). These changes are closely linked to the agricultural economy of the region, particularly related to rice cultivation, to the spread of nature conservation concerns and the reestablishment of natural areas, and to a diversification of economic activities.

Potential Drivers of Changed Transmission

Attributes of the elements influencing the disease transmission system (the parasite, competent mosquito vectors, habitats for their breeding, and susceptible people) can vary at different temporal scales. In this study, we test the effect of six potential drivers that highlight how the system is expected to react to different changes in biological attributes, agricultural practices, land use, tourism activities, and climate.

Driver 1. People–vector contacts largely depend on trophic preferences of *An. hyrcanus*.

Entomological parameters are sometimes difficult to measure in the field or in the lab. One example is the anthropophily, defined as the proportion of blood meals taken from people as opposed to other animals, such as horses and bulls not infected with human malaria. This parameter was difficult to estimate based on field data because very few blood-fed *An. hyrcanus* females were collected (Ponçon et al., 2007a). Among the nine blood meals processed, none was from people. However, *An. hyrcanus* demonstrated a very aggressive behavior to people in the field. *An. hyrcanus* is, therefore, thought to have an opportunistic trophic behavior (Ponçon et al., 2007a) and modify its biting preference depending on the proportion of bulls, horses, and humans present in the field. This will influence the people–vector contacts.

Driver 2. Water management practices for rice cultivation has an impact on disease risk transmission by controlling the seasonal distribution of mosquitoes.

Rice cultivation is the main agricultural activity in the Camargue. Rice cultivation requires a large quantity of freshwater, particularly from June to August (Dervieux, 2005). In the study area, a canal network provides water. Rice fields are flooded and drained artificially using private pumping. *An. hyrcanus* larvae develop in rice fields with water and rice plants covering the water surface, i.e., from mid-June to the end of August (Ponçon et al., 2007b). With climate change, the growing season of rice could be extended, which could allow shifting earlier or later the flooding period of rice fields. It is expected to have an impact on the temporal distribution of *An. hyrcanus* and therefore a small impact on the total human biting rate.

Driver 3. Promoting nature conservation by marsh restoration will increase the risk of malaria reemergence.

The drainage of marshes often has been cited as one of the reasons why malaria was eradicated from Europe (Reiter, 2000; Kuhn et al., 2003; Willott, 2004). Since 1960, a large part of the study zone was drained and the management of water was controlled for agricultural purposes, particularly rice cultivation. With the increasing concerns for nature conservation in the Camargue (Dervieux, 2005), this trend could be reversed. Several parcels became departmental or state properties for nature conservation and restoration of wet areas (Petit and Rivière-Honegger, 2006). They were not subjected to insecticide treatment. Simultaneously, horses and bulls were increasingly grazing in marshes, which are central to the Camargue identity. These areas also are used for hunting, another local tradition, because the marshes attract various species of migratory birds (Dervieux, 2005). Such a return to more natural water regimes typical of wetlands and marsh vegetation is believed to increase the abundance of mosquitoes and associated mosquito-borne diseases (Willott, 2004).

Driver 4. More frequent flood events, caused by an increase in precipitation and sea-level rise, will increase the risk of malaria reemergence.

With climate change and consequent sea-level rise (1.5–2 mm/year), the number of flood events is expected to increase in the Camargue. Water flows between the sea, the ponds, and channels of the Camargue are increasingly difficult to control (Dervieux, 2005). The Rhone delta was affected by several floods caused by the breaking of sea walls during the last 15 years (1993–1994, 2001, 2002, and 2003) (Dervieux, 2005). These events are expected to cause a rapid increase in mosquito abundance.

Driver 5. An increase in mass tourism will increase people–vector contacts.

Thanks to its emblematic natural areas, the Camargue has an international recognition for its landscape beauty. Tourism and leisure activities became a major activity in this region. Various touristic activities developed during the last decades, which include visits to farms, rice paddies and marshes, ecotourism, and bull fights, have allowed farmers to diversify their incomes. The local tourism should be distinguished from the more international tourism or mass tourism. The former includes tourists from the region that are present in the Camargue for a short stay and who mainly practice hunting and fishing, whereas the latter includes tourists from other regions of France and from foreign countries who come in the Camargue for a longer stay to visit the region, and who generally stay in a campsite or hotel. Mosquitoes are expected to affect differently these two categories of tourists, because they are not visiting the same locations and their protection levels differ. An increase in mass tourism is thought to have a larger impact on people–vector contacts.

Driver 6. Globalization of tourism will increase the risk of malaria reemergence in the Camargue.

With the globalization of tourism, an increasing number of tourists from malaria-endemic countries come to France and an increasing number of French tourists travel in endemic areas. The intensification of exchanges with endemic areas is expected to increase the number of malaria cases imported in the area and therefore the risk of malaria reemergence.

Methods

A spatially explicit and dynamic multiagent simulation (MAS), called MALCAM, was designed to simulate spatial and temporal variations in contact rate between people and potential malaria vectors in the Camargue. This contact rate is called "actual biting rate" (ABR) and is defined as the actual number of bites given to human agents. This is different from the "potential biting rate" (PBR), defined as the number of bites that could be potentially given to human agents. The latter depends on the density of host-seeking female mosquitoes, whereas the former is the fraction of these mosquitoes that actually encounter a human host in their quest for a blood meal (Linard et al., 2008). The broader objective of this model was to understand the factors that control variations in ABR and thus the risk of reemergence of malaria in the region. A detailed description of the model, its sensitivity analysis, and validation is provided in Linard et al. (2008). Here, this model was used to simulate the effect of changes in the drivers described above. This section consists of a brief description of the model and its improvements compared with the previous version, and of the method used to test the effect of potential drivers with the MALCAM model.

MALCAM Model

The MALCAM model represents interactions between the different agents that could influence malaria transmission in the Camargue: people, mosquitoes, animal hosts, and the landscape. This dynamic simulation model is an integrated representation of biological, geographical, and human components of the system. The model was developed using NetLogo, a free programmable environment for the modelling of complex phenomena (Wilensky, 1999). It focuses on *An. hyrcanus*, the only current potential malaria vector in the Camargue (Ponçon et al., 2007a). Because *An. hyrcanus* only bites at night and during evenings, daytime hours were excluded from the model. The model covers a complete season of mosquito activity, from May to October. Time is modelled as discrete time-steps, called periods. Three periods relevant for *An. hyrcanus*-human interactions were represented in the model: (1) from the sunset until 1 hour after sunset (period 1); (2) from 1 hour after sunset until 2 a.m. (period 2); and (3) from 2 a.m. until sunrise (period 3).

We used a land-use/cover map produced by Tran et al. (2008) based on Landsat ETM + satellite data from 2001 as a cellular-spatial support for the movements of and interactions between mobile agents. Cells have a spatial resolution of 30 m and are divided in five land-use classes: rice fields, vineyards, marshes and reed beds, urban areas, and other land-use/cover types. Mobile agents are divided in two classes: humans and other animals. The latter class includes horses and bulls, which also are potential hosts for *An. hyrcanus*. We divided human agents in different classes according to their activities: rice growers, wine growers, hunters, local inhabitants, and tourists who stay at the hotel or campsite. We only considered human activities taking place during the evening and nighttime periods. Each mobile agent is located on a 30-m × 30-m cell and move on these cells with respect to its activity and the associated land use. Human attributes, such as the protection level against mosquito bites and the location in a landscape unit at a particular time, depend on the activity and land use. Given the large number of mosquitoes, we considered the population of mosquitoes located on one cell as a single agent instead of considering each individual mosquito as an agent. Procedures related to the development and movement of mosquitoes are thus represented by cell population values.

The user interface of the MALCAM model in NetLogo displays spatial and temporal variations of the abundance of *An. hyrcanus*, the potential biting rate (PBR) (i.e., the number of mosquito bites that could potentially reach human agents), and the actual biting rate (ABR) (i.e., the number of bites actually reaching human agents). Areas with a high human biting rate at certain times of the year and groups of human agents most affected by mosquito bites can be identified. Global level outputs, such as the total number of human–vector contacts (total ABR) during the season, also are computed.

The dynamics of the system is driven by interactions between people, mosquitoes, animal hosts, and land. Mosquitoes seek to bite a host on their cell, and people use protective measures to avoid being bitten. All decision rules and equations forming the model are presented in Linard et al. (2008). All the tests, sensitivity analysis, and validation based on field observations performed with the MALCAM model gave enough confidence to use it for simulating changes in potential drivers of people–vector contacts and risk of malaria reemergence in the Camargue (Linard et al., 2008).

Improvement of the Protection Level of People

A rule has been added to the model to improve the representation of the protection level of people, which was determined by simple Gaussian distributions in the previous version. In nonendemic areas, two main factors influence people's decision to protect themselves: the harmful effect felt and the comfort level desired (Coosemans and Guillet, 1999). The harmful experience depends on the PBR at the location of the agent and on the species involved. Species, such as *Aedes* and *Culex*, are noisier and their bites are more painful compared with *Anopheles* (Schoepke et al., 1998; Pages et al., 2007). *An. hyrcanus* is the only competent malaria vector in the region. Because people do not differentiate between species, abundant *Aedes* and *Culex* populations will encourage protection. On the contrary, a decrease in abundance of these species could induce a feeling of low mosquito pressure and thus to a relaxing of protection measures—even though *Anopheles* would still be biting (Pages et al., 2007).

In the Camargue, *Aedes caspius* is the most abundant—41% of collected mosquitoes in the Carbonnière (Ponçon et al., 2007b)—and most harmful species for people, against which larviciding is performed. The eggs of *Aedes* species resist to desiccation and hatch immediately after being flooded (Kettle, 1995). The emergence of *Aedes* follows a precipitation or a flood event and causes an immediate reaction in the population, particularly in the tourist sector (Ponçon et al., 2007b). In case of a very large emergence, tourists tend to leave the zone and tourist activities are cancelled.

We therefore represented in the model the abundance of the harmful *Aedes* mosquitoes. Even though they are not competent vectors, their presence influences the adoption of protection measures by human agents. The relationship between the level of abundance of painful mosquitoes, a variable ranging from 0 to 10, and the average protection level of people was set as an exponential function (Figure 1). The model still distinguishes the protection level of tourists (campers and tourists staying at the hotel) and local people, because social surveys revealed different behaviors for these categories of people (Linard et al., 2008). We considered that the maximum level of protection of people is 0.95, because people are never fully protected. We considered that 50% of the tourists leave the zone whenever the abundance of *Aedes* reaches at least level 8.

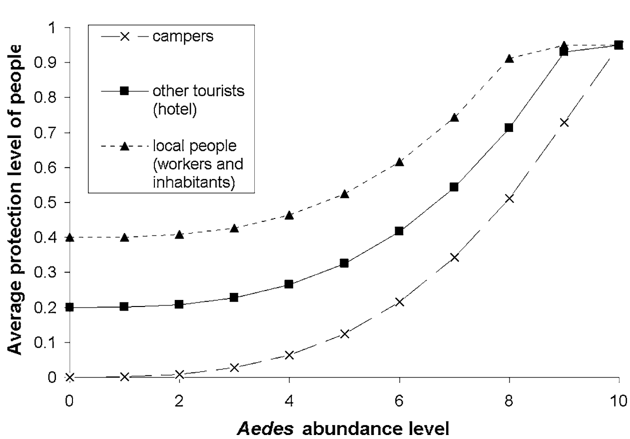

Figure 1. Evolution of the average protection level of people according to the level of abundance of *Aedes*.

Scenario Analysis

In the basic MALCAM model described earlier, initial conditions were mainly based on recent field data. To simulate the effect of changes in the drivers, scenarios were developed by varying the value of input variables or parameters. The model output was then compared with a baseline. A summary of all the scenarios is presented in Table 1. We ran the model 50 times for each scenario to account for stochasticity and we computed average results. For drivers 1 to 5, we compared the total ABR computed under each scenario. For the driver 6 and drivers 5 and 6 combined, we compared the total number of new human cases of infection.

Driver 1

In the basic model, we considered that mosquitoes disperse homogeneously in all directions until they reach a pixel with a host, with a maximal dispersal distance of 2,100 m (Linard et al., 2008). If there is more than one host within a pixel, mosquitoes select randomly one host to bite. Human and animal hosts have the same probability of being bitten (i.e., the anthropophily h is 0.5). Given that the actual rate of anthropophily of *An. hyrcanus* is unknown, we tested five alternative scenarios. In two scenarios, we considered that *An. hyrcanus* had a preference for animals, with h being 0.25 (scenario 1.2), or for humans, with h being 0.75 (scenario 1.3). In two other scenarios, when both human and animal hosts are present on their cell, mosquitoes always choose to bite animals (scenario 1.1) or humans (scenario 1.4). In a fifth scenario, mosquitoes only bite humans ($h = 1$). They keep moving across cells until they find a human agent (scenario 1.5).

Driver 2

In the basic model, rice fields are flooded at the beginning of May. Vegetation appears 1.5 months later, at mid June, and is drained at the end of August. We compared the impact of four other scenarios in which rice fields are flooded and drained 1 month earlier, a half-month earlier, a half-month later, and 1 month later (scenarios 2.1 to 2.4) in response to climate change.

Table 1. Summary of scenarios implemented

Scenario	Changing model inputs	New value
1.1	Anthropophily	"If they have the choice: only animals"
1.2		0.25
1.3		0.75
1.4		"If they have the choice: only humans"
1.5		1
2.1	Flooding date of rice fields	01/04
2.2		15/04
2.3		15/05
2.4		01/06
3.1	Area of marshes	+50%
	No. of horses and bulls	
	No. of hunters	
4.1	Date of flood event	01/07
4.2		15/07
4.3		01/08
4.4		15/08
5.1	No. of hunters	+50%
5.2	No. of campers	+50%
	Location of the new campsite	Location 1
5.3	No. of campers	+50%
	Location of the new campsite	Location 2
5.4	No. of hotel-based tourists	+50%
	Location of the new hotel	Location 1
5.5	No. of hotel-based tourists	+50%
	Location of the new hotel	Location 2
6.1	No. of infective campers introduced	10
6.2		20
6.3		30
6.4		40
6.5		50
6.6	No. of infective hotel-based tourists introduced	10
6.7		20
6.8		30
6.9		40
6.10		50
7.1	No. of campers	+50%
	Location of the new campsite	Location 1
	No. of infective campers introduced	10
7.2	No. of campers	+50%
	Location of the new campsite	Location 2
	No. of infective campers introduced	10

Driver 3

We tested a scenario of nature conservation that includes changes in the extent of marshes, with impacts on animal populations and the number of hunters (scenario 3.1). In this scenario, we increased by 50% simultaneously the marsh area, the horse and bull populations, and the number of hunters. We expanded the area of current marshes to adjacent nonmarsh cells, whatever their initial land use (except for urban). We then imported this updated land-use map in the MAS.

Driver 4

We tested the impact of a large precipitation or flood event on the actual biting rate. We assumed that the level of abundance of *Aedes* is 5 in normal times and that it reaches the level 10 after a precipitation or flood event. This level then decreases linearly with time until reaching the level 5 after 25 days. This is associated with a decrease in the average protection level for the different categories of people (Figure 2). We compared the impact of flood events occurring at different dates: July 1, July 15, August 1, and August 15 (scenarios 4.1 to 4.4).

Driver 5

In the model, we distinguished three categories of tourists with evening activities: campers, tourists staying at the hotel, and hunters. We compared three different scenarios in which we increased successively by 50% the number of hunters (scenario 5.1), the number of campers (scenarios 5.2 and 5.3), and the number of tourists staying at the hotel (scenarios 5.4 and 5.5). New campers and hotel-based tourists were added in a new campsite or hotel. We tested two possible locations for these new campsites and hotels that were selected in grasslands for the campsite and in the suburban zone for the hotel (Figure 3).

Driver 6

The MALCAM model simulates the spatial and temporal distribution of the human biting rate. However, the model can also simulate malaria transmission by introducing infected people or mosquitoes in the area. To test last driver, we implemented scenarios where various numbers of

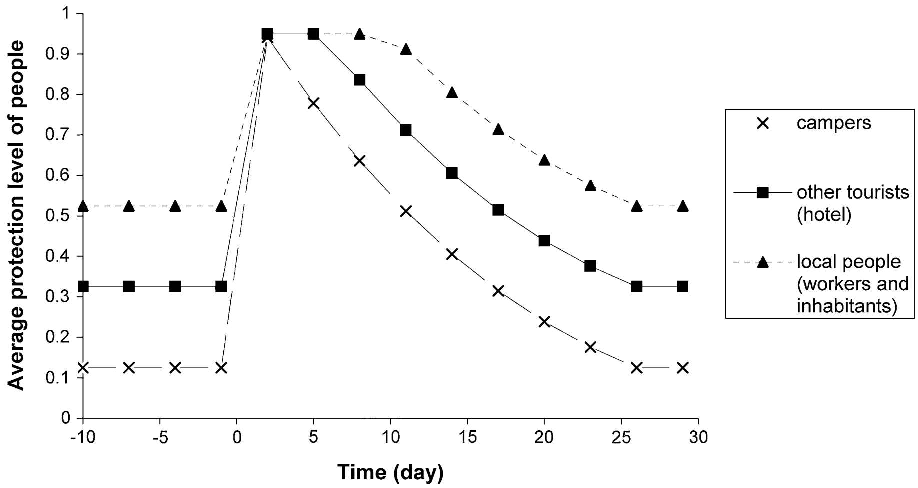

Figure 2. Changes in the average protection level of people after a flood event at time 0.

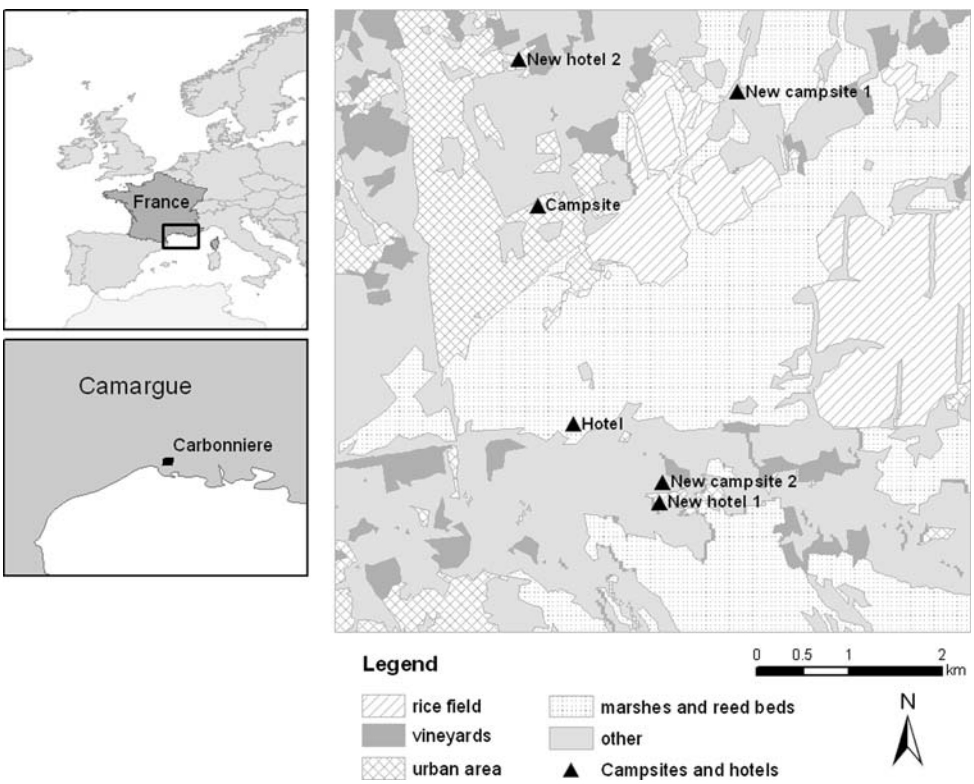

Figure 3. Localization of current and new hypothetical campsites and hotels in the "Carbonniere" study area in the Camargue region, southern France. New campsites and hotels are used in scenarios 5.2, 5.3, 5.4, 5.5, 7.1 and 7.2.

infective tourists were introduced in the area at the beginning of the season. The susceptible human agents were assumed to have no immunity. We only considered *Plasmodium vivax* infections as Ponçon et al. (2008) estimated the risk of *P. vivax* transmission as more than 100 times higher than the risk of *P. falciparum* transmission. Humans and *An. hyrcanus* can be in three different consecutive states: susceptible, infected, or infectious. Because the model only covers one season of 6 months, the recovery rate was not taken into account and infectious individuals remain infectious throughout the rest of the year.

In addition to the contact rate, we calculated the probability of malaria transmission for each contact between an infectious and a susceptible agent. We added two parameters to the model: (1) the susceptibility of mosquitoes to *P. vivax*, i.e., the proportion of female mosquitoes developing parasites after an infective blood meal, and (2) the susceptibility of humans, i.e., the probability of developing a new infection after an infectious bite. These parameters were fixed at, respectively, 0.2 (Ponçon et al., 2008) and 0.5. Additional outputs can be extracted from the model: the number of infected people, the number of infected *An. hyrcanus*, and their distribution in space and time. We tested ten scenarios where we varied the number of infectious tourists introduced (10, 20, 30, 40, or 50) and whether these infective tourists stay overnight in a hotel or campsite (scenarios 6.1 to 6.10).

Drivers 5 and 6 Combined

As an increase in mass tourism favors the importation of malaria cases in the Camargue, we also combined drivers 5 and 6 in additional scenarios. We tested the effect of an increase in the number of campers by 50% combined with the introduction of ten infectious tourists among them. We implemented scenarios in which ten tourists from the new campsite 1 (scenarios 7.1) or ten tourists from the new campsite 2 (scenarios 7.2) were infectious throughout the season.

Results

Driver 1. People–vector contacts largely depend on trophic preferences of *An. hyrcanus*.

The simulation outputs show little change in response to changes in this driver. The total ABR on people was not significantly different in scenarios 1.1 to 1.5 compared with basic conditions (with all p values from t tests >0.05; Figure 4). Whatever the level of anthropophily, no impact was observed on people–vector contacts. Given their limited dispersal distance and the low density of hosts in the surroundings of rice fields, *An. hyrcanus* seem to be constrained to bite the first host that they find, whether it is a human or animal host. There was no major difference between categories of human agents. In their probabilistic approach to the risk of malaria reemergence in Southern France, Ponçon et al. (2008) also concluded that the anthropophily had a minor impact on the risk estimate.

Driver 2. Water-management practices for rice cultivation has an impact on disease risk transmission by controlling the seasonal distribution of mosquitoes.

Changes in this driver induced changes in the seasonal distribution of mosquitoes. The variation of the flooding date of rice fields also had an important impact on the ABR and thus on disease risk transmission. The basic model with the current date of flooding of rice fields (May 1) provided a higher total ABR than scenarios 2.1, 2.2, 2.3, and 2.4 (Figure 4). Rice fields flooded 1 month earlier or 1 month later induced considerable reductions in the total ABR (72% and 81%, respectively). This impact is much larger than would be expected from changes in seasonality alone. This could be the result of the combined effect of temperature and the number of people present in the zone. Temperature influences the length of the gonotrophic cycle and the development rate of mosquitoes. It is highest in June, July, and August. With the current conditions of water and vegetation in rice fields, larvae develop from mid June to late August, which corresponds exactly to the period of the highest temperatures. The number of people present in the zone also varies along the season and is the highest in July and August, particularly the number of tourists. Very high contact levels are achieved when the peak of mosquito activity corresponds with the peak of activity of people.

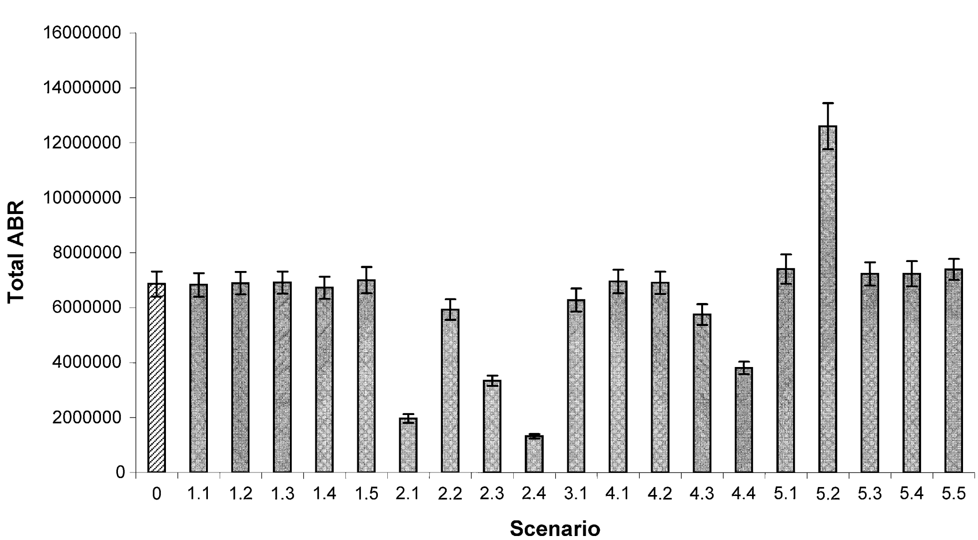

Figure 4. Total actual biting rate (ABR) for the basic model (scenario 0) and scenarios related to drivers 1 to 5. Total ABR was calculated as the average of 50 simulations for each scenario. Error bars represent ± 1 standard deviation from the mean.

Driver 3. Promoting nature conservation by marsh restoration will increase the risk of malaria reemergence.

The simulation outputs show a decrease in the risk of malaria reemergence in response to changes in this driver. With the nature conservation scenario (scenario 3.1), the total ABR decreased by 9% compared with the baseline scenario (Figure 4). Because rice fields are the main breeding sites for *An. hyrcanus*, the expansion of marshes to the detriment of rice fields—among other land uses—limited *An. hyrcanus* abundance. However, *An. hyrcanus* have strong adaptation abilities and could extend their potential breeding sites in the future. The simulated land-use changes also induced a decrease in the number of people passing near rice fields and therefore a lower contact rate. The ABR decreased for all categories of people except for hunters (+34%).

Driver 4. More frequent flood events, caused by an increase in precipitation and sea-level rise, will increase the risk of malaria reemergence.

The simulation outputs show a status quo or a decrease in the risk of malaria reemergence in response to changes in this driver. The total ABR was almost identical in the baseline scenario and in scenarios 4.1 and 4.2, with p values from t tests of 0.69 and 0.83, respectively (Figure 4). However, the total ABR decreased by 17% in scenario 4.3 and by 45% in scenario 4.4. Flood events led to a decrease in people–vector contacts and thus in the risk of malaria reemergence, but only when these events appeared in August. We can observe in Figure 5 that the ABR decreased drastically just after the flood event. With floods, the abundance of *Aedes* suddenly increased, which encouraged people to protect themselves. When *Aedes* mosquitoes progressively disappeared, the protection level of people also decreased. Flood events had a bigger impact on the ABR in August, when *An. hyrcanus* are abundant.

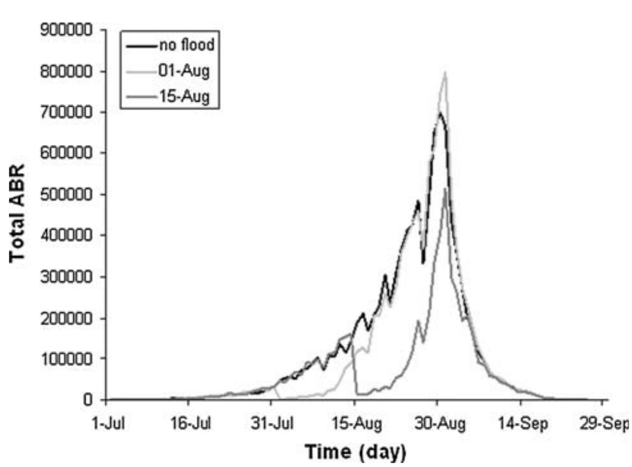

Figure 5. Total actual biting rate (ABR) at period 1 throughout the season for the basic model (no flood) and for scenarios 4.3 (flood on August, 1) and 4.4 (flood on August, 15).

Driver 5. An increase in mass tourism will increase people–vector contacts.

The simulation outputs confirm the expected increase in people–vector contacts in response to changes in this driver. The total ABR increased slightly in scenarios 5.1, 5.3, 5.4, and 5.5, with an increase from 6% to 9% compared with the baseline (Figure 4). However, in scenario 5.2, increasing the number of campers led to a much larger increase in total ABR (+84%). The increase in total ABR induced by an increase in the number of campers or tourists staying at the hotel depends on the location of new tourists. In scenario 5.2, the new campsite was situated closer to rice fields than the older campsite (Figure 3, new campsite 1) and the ABR of campers increased by more than 400%. With the second location of the new campsite (scenario 5.3), the increase in the ABR of campers was only 29%. The ABR of tourists staying at the hotel increased by 46% with the first location of the hotel (scenario 5.4) and 101% with the second location (scenario 5.5). The ABR of hunters increased proportionally with the number of hunters present in the study zone: a 50% increase in the number of hunters induced a 55% increase of their ABR. The number of bites per hunter is more than 30 times larger than the number of bites per person for other tourists, although they adopt a higher protection level. Isolated hunters located in marshes concentrate many of the bites. However, an increase in the number of hunters had a limited impact on the total ABR, because the number of hunters is very small compared with other categories of people.

Driver 6. Globalization of tourism will increase the risk of malaria reemergence in the Camargue.

The simulation outputs confirm the increased risk of malaria reemergence in response to changes in this driver. Infectious tourists visiting the Camargue, which becomes more likely with globalization, increased the risk of malaria reemergence by introducing the *Plasmodium* parasite in the system. However, this risk was extremely low, particularly when infectious tourists stayed overnight in the hotel (Figure 6, scenarios 6.6 to 6.10). When 50 infected hotel-

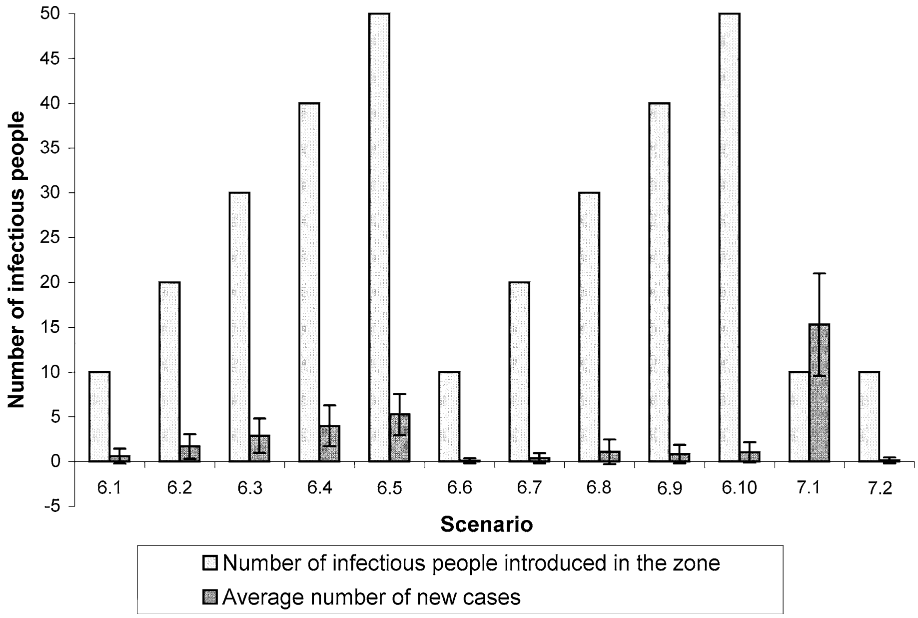

Figure 6. Number of infectious people introduced in the zone and total number of new infections predicted by the MALCAM model for scenarios 6.1 to 7.2. The number of new infections was calculated as the average of 50 simulations for each scenario. Error bars represent ± 1 standard deviation from the mean.

based tourists were introduced in the zone, the average number of new malaria cases was only 1 for the entire season (scenario 6.10). When the 50 infectious tourists were camping overnight, and were thus more exposed to mosquito bites, the transmission risk was slightly higher and reached an average of 5 new cases for the entire season (scenario 6.5). Newly infected people were mainly local inhabitants (42% of new cases), campers (39% of new cases), and hotel-based tourists (18% of new cases). New infections were mainly transmitted between the campsite and the rice fields, which is the most populated area close to rice fields (Figure 7).

Drivers 5 and 6 combined. The effect of combined changes in drivers 5 and 6 on the number of new cases over the season strongly differs depending on the location of the infectious people. When 10 infectious people were present in campsite 2 throughout the season (scenarios 7.2), the average number of new cases was only 0.12. However, when 10 infectious people were localized in campsite 1, which is closer to rice fields (scenario 7.1), the average number of new cases reached 15. Simulation outputs from scenario 7.1 showed a higher average number of new cases compared with the number of infectious tourists introduced in the area (Figure 6).

Discussion

To explore the potential role of the biology of mosquitoes, land-use changes, and changes in tourist activities for the risk of malaria reemergence in the Camargue, we formulated scenarios of possible future changes. Simulations with the MALCAM model allowed implementation of these scenarios. Results from our model simulations suggested that major processes of malaria transmission in the Camargue are represented in the model, that it is sensitive to plausible external changes, and that it provides consistent simulation outputs. Yet, results from our model simulations should not be interpreted in strict quantitative terms but rather in terms of general trends and comparison between scenario outputs.

Simulation outputs related to two potential drivers showed the expected effect (drivers 5 and 6), whereas four other not (drivers 1, 2, 3, and 4). The complexity of interactions between land – mosquitoes – animal hosts – human hosts – parasites and the difficulty in apprehending the system behavior without computer tools explains why changes in some factors that were intuitively viewed as drivers of disease reemergence led to unexpected results. Scenarios highlighted for instance the importance of the seasonality (driver 2: peaks of mosquito and people activity must correspond to reach high contact levels) or the negative feedback existing between the ABR and the abundance of other mosquito species, via the protection level of people (driver 4). The effect of changes in driver 3 led to unexpected results because the vector species in the Camargue has changed through history. Until the early 20th century, *Anopheles atroparvus* was the main malaria vector in the Camargue (Rodhain and Charmot, 1982; Ponçon et al., 2007c). Nowadays, this competent vector species became

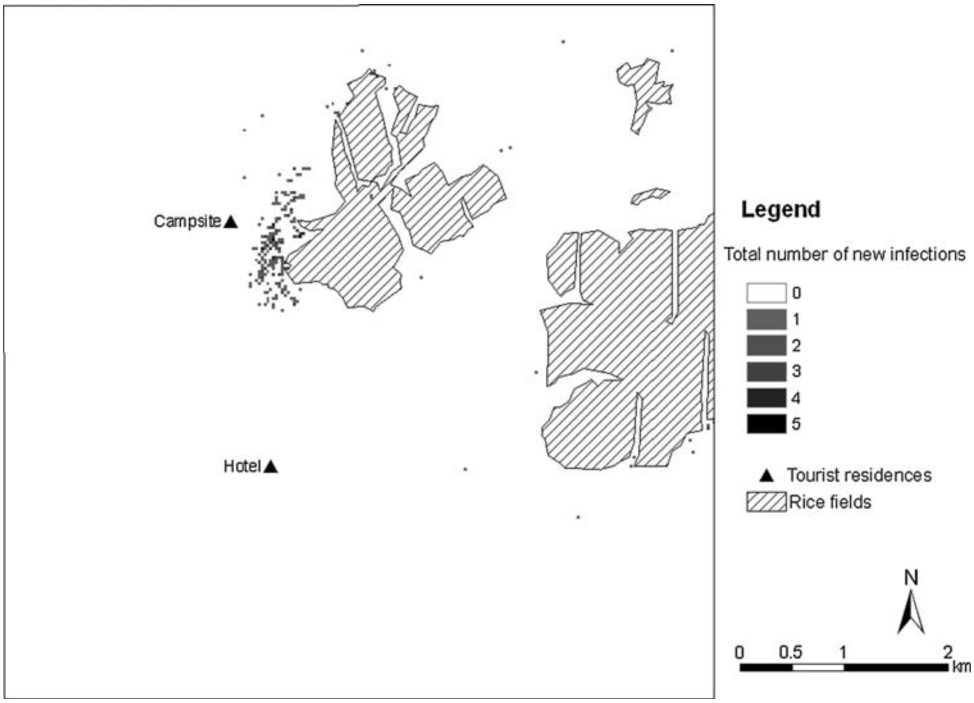

Figure 7. Spatial distribution of new malaria cases predicted by the MALCAM model in the "Carbonniere" study area in the Camargue region, southern France. These predictions are based on scenario 6.5, which introduced 50 infective campers in the study zone. The map shows the total number of new infections from 50 simulations.

rare, whereas *An. hyrcanus*, less efficient, became very abundant, which is mainly due to land cover changes (Ponçon et al., 2007b, c). Currently, an increase in marsh area is not associated with a risk of malaria reemergence, unless there is another change in vector species.

Most scenarios were implemented by varying individual (or just a couple of) parameters or input variables. In reality, multiple changes could combine their effect. For instance, drivers 5 and 6 were combined to assess the effect of an increase in mass tourism combined with an increase in the number of malaria cases imported. Changes in input variables could induce changes in other factors. If climate change allows rice growers to change the flooding period of rice fields (because of higher temperatures in September, for example), these changes also could influence other factors, such as the development and mortality rates of mosquitoes, the length of their gonotrophic cycle, and the number of visitors outside the summer period.

The scenarios based on infectious people arriving in the zone (driver 6) go beyond the actual biting rate (i.e., people–mosquito contacts) and represent the risk of infection transmission. This risk is strongly related to the ABR. Figure 4 showed that scenario 5.2 provided the highest ABR and adding infectious people to this scenario induced a high number of new cases (scenarios 7.1). The output of scenarios related to driver 6 is comparable to the Basic Reproductive Rate (R_0), which quantifies the average number of new cases of the infection that will arise from the introduction of an infective host into a susceptible population, in the absence of immunity (Mcdonald, 1957). Our agent-based modelling approach represents explicitly the spatial and temporal distributions of these new cases, at the landscape scale. Transmission was concentrated in the zone of the highest people–vector contacts. Results from changes in driver 6 showed that the risk of malaria reemergence is very low in the Camargue. New cases emerged only under unlikely conditions. The probability that, throughout the summer, at least 50 infectious persons would be camping not far from rice fields is indeed very low. Moreover, the number of new cases predicted was generally extremely low compared with the number of infectious people introduced. This suggests that the infection would rapidly disappear, given a low contagious potential. However, in scenario 7.1 that combined the effect of drivers 5 and 6 and involved the establishment of a new campsite close to rice fields, the number of new cases per infectious person introduced in the area was 1.53 in average, indicating a higher contagious potential. As soon as a few cases would be reported, people would respond by increasing their protection level, avoiding altogether the region, or developing public health policies, such as treating or isolating parasites carriers and spraying insecticide to control vectors. The tourism industry also would respond quickly, as they currently do when there is a surge in the population of *Aedes*, an aggressive mosquito but a non-competent vector.

The results from the scenario analysis related to the six potential drivers allow formulation of pathways of possible malaria reemergence in the Camargue. Model simulations show that malaria could reemerge in the Camargue only under a combination of particular conditions. First, *Plasmodium* has to be introduced in the system. Only the arrival of a large population of infectious people or infectious mosquitoes could induce autochthonous transmission. Second, there must be a contact area where vectors and people meet. The proximity between rice fields, the main breeding sites for *An. hyrcanus*, and land uses associated with evening or nighttime human activities is essential. Third, vectors and people must be present not only at the same place but also at the same time for contacts to occur: their peaks of activity must be synchronized. In addition to these three minimum conditions, other factors can favor people–vector contacts and the risk of malaria reemergence at the landscape scale: a decrease in the abundance of other aggressive mosquitoes inducing a relaxing of protection measures, the establishment of a new campsite close to rice fields, or an increase in mass tourism. Model simulations also highlighted factors that could limit people–vector contacts, such as a flood event followed by a sudden increase in the protection level of people or a change in the flooding period of rice fields. Among all the factors that can limit people–vector contacts and thus prevent malaria transmission, changes in the flooding period of rice fields seemed to be the most efficient, with a potential reduction of more than 80% of the total ABR. It also is a low-cost preventive measure. This study did not integrate response strategies involving public health authorities: information, prevention, or improvement in early diagnoses and treatment.

Conclusions

The risk of malaria reemergence is low in the Camargue. If the disease would reemerge, it would be the result of an unlikely combination of unfavorable biological, land use, and socioeconomic and climatic conditions. High levels of people–vector contacts are essential for a reemergence of malaria, if the parasite were reintroduced in the population. These contacts depend on a combination of factors, such as the landscape pattern, tourism activities, agricultural policies, biological evolution of mosquitoes, temperature, and flood events.

The spatially explicit and dynamic multiagent simulation of malaria transmission system (MALCAM model) that we developed allowed simulating the effect of changes in various potential drivers of vector-borne disease reemergence at the landscape scale. Interactions and feedbacks existing in the multiagent simulation between the different agents and between agents and their environment led in some cases to counterintuitive results. Scenarios were useful for assessing the impact of biological, geographical, or social changes on the risk of malaria reemergence. Results from scenario analyses may help local authorities formulate policy and may contribute to a decision-support system in public health, land use planning, or regional development. The modelling approach and scenario analysis presented could be easily extended to the possible emergence of other mosquito-borne diseases in Europe, such as West Nile virus, Chikungunya, or dengue.

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